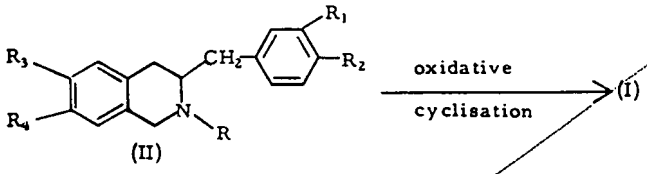
SPECIFICALLY CLAIMED

12 Cpds. (I) e.g. $R_1 = R_2 = R_3 = CH_3O$; R = H or CH_3; or R = R_2 = H; $R_3 = CH_3O$; R_1 = HO or CH_3O; all (±) racemates.

PREPARATION



(II)

(R_4 = OH, 1-6C alkoxy or benzyloxy).

Pref. (II) is dissolved in CF_3COOH-haloalkane solvent mixt., at -15 to 30°, pref. -15 to 5°C, then $VOCl_3$ or VOF_3 added as oxidising agent. The mixt. is reacted at -10 to 0°C for 0.5-2 hr. Pref. 2.5 moles oxidising agent are used per mole (II). Pref. $VOCl_3$ is used if (II) contains phenolic OH gps. and VOF_3 otherwise. (I; R = H) can be alkylated etc. conventionally to introduce other values of R.

EXAMPLE

5.63 g 2-Methyl-6,7-dimethoxy-3-veratryl-1,2,3,4-tetrahydroisoquinoline were dissolved in 60 ml CF_3COOH (ice cooling), then the soln. treated, with exclusion of moisture under N_2 at -15 to -10°C, with 4.2 g VOF_3 in 20 200 ml CF_3COOH over 5 min. The mixt. was stirred for 1 hr. at -15 to -10°C, then solvent distd. out. The residue was mixed with water, extd. with $CHCl_3$, and the extracts washed with dil. NH_4OH, dried and evapd. Crystn. of the residue from MeOH ether gave 4.55 g (85%) (±)-1,2,3,4-tetrahydro-7,10,11-trimethoxy-3-methyl-6-oxo-2,8a-methano-6H-dibenz(c,e)azocine, m.pt. 168.5-170°C. (29pp1251).

(E) ISR: 4 Journal References.

EP--11483

38728C/22 B05 BEEC 16.11.78

BEECHAM GROUP LTD *EP--11-489

16.11.78-GB-044839 *(28.05.80)* A61k-09/46 A61k-31/16 A61k-33

Effervescent analgesic powder compsn. esp. for treating migrane - comprises paracetamol DC and metoclopramide

D/S: E(BE, CH, DT, FR, GB, IT, NL, OE, SW).

An analgesic effervescent powder comprises paracetamol D.C. (I) and metoclopramide (II) or its acid addn. salt, in wt. ratio (I):(II) of 50-250:1, pref. 80-120:1. Amt. of (II) or salt is pref. 0.05-0.4 wt.% of powder. Pref. effervescent materials are $NaHCO_3$ and NaH_2 citrate or Na_2H citrate. Pref. units contain 0.4-0.6g (I) and 4-6 mg (II) or salt.

The powder in aq. soln. is also claimed.

USES

(II) is a known potentiator for orally administered analgesics. Compsn. is esp. useful for treating migraine headaches and gives relief of associated gastrointestinal symptoms.

PREPARATION

I) and (II) may be wet granulated together, dried, and mixed with effervescent materials.

B(5-C4, 10-B1A, 10-C2, 10-D3, 12-C9, 12-D1, 12-M6, 12-M11).7 G7

EXAMPLE

5.25 mg of (II) hydrochloride B.P. (60 mesh), 10 mg sweetener and 20 mg flavouring (30 mesh), 158 mg Na_2CO_3 (50 mesh) and an equal vol. of (I) (96% pure) (30 mesh) were mixed for 5 min. in a planetary mixer at < 40% R.H. Further (I) to a total of 520 mg was added followed by 5 min. mixing, then 923 mg of anhyd. citric acid (30 mesh) were added followed by 5 min. mixing, and finally 1250 mg of $NaHCO_3$ (30 mesh) were added followed by 30 min. mixing. The mixt. was then filled into a sachet. (12pp949).

(E) ISR: FR2187312; BE-769156; FR2013552; US3136692; FR2085730; GB1442159; 6 Journal References.

38728C EP--11489

38729C/22 B05 BEEC 16.11.78

BEECHAM GROUP LTD *EP--11-490

16.11.78-GB-044842 *(28.05.80)* A61k-09/20 A61k-31/16

Analgesic tablet comprising analgesic agent and metoclopramide or salt - esp. useful for treating migraine headache

D/S: E(BE, CH, DT, FR, GB, IT, NL, OE, SW).

An analgesic tablet comprises an analgesic agent (I) and metoclopramide (II) or its acid addn. salt in wt. ratio (I) : (II) of 50-250:1, esp. 80-120:1. Pref. (I) is aspirin or paracetamol, esp. paracetamol D.C.

Amt. of (II) or salt is pref. 0.25-2.0 wt.% of tablet. Pref. tablet contains 0.4-0.6 g of (I) and 4-6 mg (II) or salt. Pref. the tablet is made by direct compression of a powder mixt. of (I) and (II).

USES/ADVANTAGES

(II) is a known potentiator for orally administered analgesics. Compsn. is esp. useful for treating migraine headaches and also gives relief of associated gastrointestinal symptons.

DETAILS

Usual lubricants, compression aids, disintegrants, etc. may be present.

B(10-B1A, 10-C3, 10-D3, 12-C9, 12-D1, 12-M11).6 G8

EXAMPLE

125 mg of Avicel PH102 (30 mesh) (disintegrant/compression aid), 5.25 mg of (II).HCl.H_2O (60 mesh) and 130 mg paracetamol D.C. (30 mesh; 96% pure) were mixed for 10 min. in a planetary mixer. A mixt. of Aerosil 200 (30 mesh) and an equal vol. of paracetamol together with further paracetamol to a total of 390 mg (520 mg in tablet) were added to the mixt. followed by 30 min. mixing 1.3 mg of Mg stearate was added followed by 5 min. mixing, and the mixt. was compressed using a ½ inch dia. punch on a rotary tabletting machine. (8pp949).

(E) ISR: US3424842; US4097606; GB1442159; FR2247206; 5 Journal References.

38729C EP--11490